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Antioxidant Properties of Hydroxycinnamic Acids: A Review of Structure-Activity Relationships

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Abstract: Hydroxycinnamic acids (HCAs) are important phytochemicals possessing significant biological properties. Several investigators have studied *in vitro* antioxidant activity of HCAs in detail. In this review, we have gathered the studies focused on the structure-activity relationships (SARs) of these compounds that have used medicinal chemistry to generate more potent antioxidant molecules. Most of the reports indicated that the presence of an unsaturated bond on the side chain of HCAs is vital to their activity. The structural features that were reported to be of importance to the antioxidant activity were categorized as follows: modifications of the aromatic ring, which include alterations in the number and position of hydroxy groups and insertion of electron donating or withdrawing moieties as well as modifications of the carboxylic function that include esterification and amidation process. Furthermore, reports that have addressed the influence of physicochemical properties including redox potential, lipid solubility and dissociation constant on the antioxidant activity were also summarized. Finally, the pro-oxidant effect of HCAs in some test systems was addressed. Most of the investigations concluded that the presence of *ortho*-dihydroxy phenyl group (catechol moiety) is of significant importance to the antioxidant activity, while, the presence of three hydroxy groups does not necessarily improve the activity. Optimization of the structure of molecular leads is an important task of modern medicinal chemistry and its accomplishment relies on the careful assessment of SARs. SAR studies on HCAs can identify the most successful antioxidants that could be useful for management of oxidative stress-related diseases.

Keywords: Antioxidant, hydroxycinnamic acids, *in vitro*, ROS, structure-activity relationships.

OXIDATIVE STRESS AND ANTIOXIDANTS

Reactive oxygen species (ROS) are oxygen derived molecules that readily react with other compounds and macromolecules and oxidize them. Some representative examples of these species include superoxide ($O_2^{\bullet-}$), hydroxy ($HO^{\bullet}$) and peroxy ($ROO^{\bullet}$) radicals, hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) [1-4].

ROS are involved in important physiological processes such as immune response, gene expression, signal transduction and growth regulation [5, 6]; however if they are not kept under tight control by physiological antioxidant systems they will be able to oxidize and damage various biological molecules leading to a condition called oxidative stress [1, 7, 8]. In this regard, oxidative stress has been reported to be involved in the pathogenesis of diseases such as cancer [9], neurodegenerative diseases [10], stroke [11], and others [12, 13].

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Since an important source of ROS comes from environment [14], with the industrial development and the change in life style, oxidative stress related diseases need a special attention [15].

Antioxidants operate by preventing or slowing the progression of oxidative damage reactions [16, 17]. An antioxidant has been defined as "any substance that delays, prevents or removes reactive species capable of inducing oxidative damage to a target molecule" [1]. Another requirement is that the compound should also generate a more stable, and therefore less injurious, intermediate molecule upon reaction with a ROS in order to be considered as a good antioxidant [4]. With the recent findings, these definitions should be broadened to encompass also agents that are capable of sequestering transition metal ions (chelation activity), inhibition of enzymes involved in ROS production and induction of endogenous defense mechanisms such as antioxidant enzymes [18].

Large scale epidemiologic cohort studies in different populations have provided evidence that consumption of dietary antioxidants is associated with reduced risks of heart diseases and neurodegeneration [19, 20]. Although a number of interventional trials have failed to prove the usefulness of antioxidants for disease management, the use of disease spe-

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